APPLICATION

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TITLE: NEW USE FOR BUDESONIDE AND FORMOTEROL

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NEW USE FOR BUDESONIDE AND FORMOTEROL

Field of the Invention

The invention provides the use of formoterol and budesonide in the treatment of chronic obstructive pulmonary disease (COPD).

Background to the Invention

Chronic obstructive pulmonary disease (COPD) is a term which refers to a large group of lung diseases which can interfere with normal breathing. It is estimated that 11% of the U.S. population has COPD and the incidence is increasing. The two most important conditions covered by COPD are chronic bronchitis and emphysema.

Chronic bronchitis is a long-standing inflammation of the bronchi which causes increased production of mucous and other changes. The patients' symptoms are cough and expectoration of sputum. Chronic bronchitis can lead to more frequent and severe respiratory infections, narrowing and plugging of the bronchi, difficult breathing and disability.

Emphysema is a chronic lung disease which affects the alveoli and/or the ends of the smallest bronchi. The lung loses its elasticity and therefore these areas of the lungs become enlarged. These enlarged areas trap stale air and do not effectively exchange it with fresh air. This results in difficult breathing and may result in insufficient oxygen being delivered to the blood. The predominant symptom in patients with emphysema is shortness of breath.

At present moderate to severe COPD is treated with a variety of monotherapies including inhaled or orally administered bronchodilators, inhaled anti-cholinergic agents and orally administered steroids, especially corticosteroids. The problem with these treatments is that none of them is especially effective. For example, many patients with COPD have a

reversible component. Accordingly a new treatment is required for decreasing the intensity of exacerbations, thereby improving the lung function of patients suffering from COPD.

Description of the Invention

It has surprisingly been found that the combination of formoterol and budesonide is effective in treating COPD.

The combination of budesonide and formoterol reduces the number of exacerbations of COPD compared to the monotherapies using budesonide or formoterol, thereby improving the lung function of the patients. Thus, the combination of budesonide and formoterol will give greater compliance, greater efficacy, less exacerbations and/or better sleep.

The present invention also gives an increased compliance and efficacy and thereby quality of life.

According to the invention there is provided the use of a composition comprising, in admixture or separately:

(a) a first active ingredient which is formoterol, a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt;

(b) a second active ingredient which is budesonide; and

a molar ratio of the first active ingredient to the second active ingredient of from 1:2500 to 12:1,

in the manufacture of a medicament for use in the treatment of chronic obstructive pulmonary disease.

The composition used in the invention optionally additionally comprises one or more pharmaceutically acceptable additives, diluents and/or carriers. The composition is preferably in the form of a dry powder, wherein the particles of the pharmaceutically active ingredients preferably have a mass median diameter of less than 10 μm.

The invention also includes the use of a kit containing:

(i) a vessel containing the first active ingredient;

(ii) a vessel containing the second active ingredient;

(iii) a molar ratio of the first active ingredient to the second active ingredient of from 1:2500 to 12:1; and

(iv) instructions for the simultaneous, sequential or separate administration of the active ingredients to a patient in need thereof;

in the manufacture of a medicament for use in the treatment of chronic obstructive pulmonary disease.

A patient suffering from COPD can be treated by administering via inhalation a composition as defined above. Alternatively such a patient can be treated by administering via inhalation, simultaneously, sequentially or separately, (i) a dose of the first active ingredient; and (ii) a dose of the second active ingredient. The molar ratio of the first active ingredient to the second active ingredient is from 1:2500 to 12. The doses can be provided to the patient for inhalation in dry powder form.

The invention further provides the use of budesonide and of formoterol in the manufacture of a composition or a kit, as used in the invention, for use in the treatment of chronic obstructive pulmonary disease.

The first and second active ingredients of the kit used in the invention can be administered simultaneously, sequentially or separately to COPD. By sequential is meant that the first and second active ingredients are administered one after the other. They still have the desired effect if they are administered separately but less than about 12 hours apart, preferably less than about 2 hours apart, more preferably less than about 30 minutes apart, and most preferably one immediately after the other.

The molar ratio of the first active ingredient to the second active ingredient is suitably from 1:555 to 2:1 and preferably from 1:150 to 1:1. The molar ratio of the first active ingredient

to the second active ingredient is more preferably from 1:133 to 1:6. The molar ratio of the first active ingredient to the second active ingredient can also be 1:70 to 1:4.

Preferably the amount of the first active ingredient used is preferably from 2 to 120 nmol (more preferably from 7 to 70 nmol). The amount of the second active ingredient used is preferably from 0.1 to 5 μmol (preferably 0.15 to 4 μmol) or from 45 to 2200 μg, more preferably from 65 to 1700 μg.

Throughout the specification, the amount of the first and second active ingredient used relate to unit doses unless explicitly defined differently.

Suitable physiologically acceptable salts of formoterol include acid addition salts derived from inorganic and organic acids, for example the chloride, bromide, sulphate, phosphate, maleate, fumarate, tartrate, citrate, benzoate, 4-methoxybenzoate, 2- or 4-hydroxybenzoate, 4-chlorobenzoate, p-toluenesulphonate, methanesulphonate, ascorbate, acetate, succinate, lactate, glutarate, gluconate, tricarballylate, hydroxynaphthalene-carboxylate or oleate salts or solvates thereof. The first active ingredient is preferably formoterol fumarate, especially the dihydrate thereof.

When the first active ingredient is formoterol fumarate dihydrate, the amount of the first active ingredient used is suitably from 1 to 50 μg, more suitably from 3 to 30 μg.

Preferably the composition or kit used in the invention comprises unit doses of 6 μg of formoterol fumarate dihydrate and 100 μg of budesonide, or 4.5 μg of formoterol fumarate dihydrate and 80 μg of budesonide, either of which is administered up to four times a day. Alternatively the composition or kit of the invention comprises unit doses of 12 μg of formoterol fumarate dihydrate and 200 μg of budesonide, or 9 μg of formoterol fumarate dihydrate and 160 μg of budesonide, either of which is administered once or twice a day.

More preferably the composition or kit used in the invention comprises unit doses of 6 μg of formoterol fumarate dihydrate and 200 μg of budesonide, or 4.5 μg of formoterol fumarate dihydrate and 160 μg of budesonide, either of which is administered up to four times a day. Alternatively the composition or kit of the invention comprises unit doses of 12 μg of formoterol fumarate dihydrate and 400 μg of budesonide, or 9 μg of formoterol fumarate dihydrate and 320 μg of budesonide, either of which is administered once or twice a day.

Most preferably the composition or kit used in the invention comprises unit doses of 6 μg of formoterol fumarate dihydrate and 400 μg of budesonide, or 4.5 μg of formoterol fumarate dihydrate and 320 μg of budesonide, either of which is administered up to four times a day.

Preferably the active ingredient(s) are used in admixture with one or more pharmaceutically acceptable additives, diluents or carriers, preferably in an amount of from 50 μg to 25 mg per dose, more preferably in an amount of from 50 μg to 10 mg, most preferably in an amount of from 100 to 2000 μg per unit dose. Examples of suitable diluents or carriers include lactose, dextran, mannitol or glucose. Preferably lactose is used, especially as the monohydrate.

One or more of the ingredients is preferably in the form of a dry powder, more preferably a finely divided powder, e.g. micronised dry powder, most preferably an agglomerated micronised dry powder. As an alternative to agglomeration, the finely divided active ingredients may be in the form of an ordered mixture with the pharmaceutically acceptable additive, diluent or carrier. An ordered mixture comprises fine particles of an active ingredient in association with coarse particles or a mixture of coarse and finely divided particles of the pharmaceutically acceptable additive, diluent or carrier. The ingredients used in the invention can be obtained in these preferred forms using methods known to those of skill in the art. The particle size of the active ingredients is preferably less than 10 μm.

Administration may be by inhalation orally or intranasally. The active ingredients are preferably adapted to be administered, either together or individually, from dry powder inhaler(s) (DPIs), especially Turbuhaler® (Astra AB), pressurised metered dose inhaler(s) (pMDIs), or nebuliser(s).

When the active ingredients are adapted to be administered, either together or individually, from pressurised inhaler(s), they are preferably in finely divided, and more preferably in micronised form. They may be dissolved or, preferably, suspended in a liquid propellant mixture. The propellants which can be used include chlorofluorocarbons, hydrocarbons or hydrofluoroalkanes. Especially preferred propellants are P134a (tetrafluoroethane) and P227 (heptafluoropropane) each of which may be used alone or in combination. They are optionally used in combination with one or more other propellants and/or one or more surfactants and/or one or more other excipients, for example ethanol, a lubricant, an anti-oxidant and/or a stabilising agent.

When the active ingredients are adapted to be administered, either together or individually, via nebuliser(s) they may be in the form of a nebulised aqueous suspension or solution, with or without a suitable pH or tonicity adjustment, either as a unit dose or multidose device.

The composition or kit used in the invention may optionally be administered as divided doses from 1 to 4, and preferably once or twice a day.

The invention is illustrated by the following Examples which are not intended to limit the scope of the application. In the Examples micronisation is carried out in a conventional manner such that the particle size range for each component is suitable for administration by inhalation. Turbuhaler is a trademark of Astra AB.

Example 1

6 Parts by weight of formoterol fumarate dihydrate was mixed with 794 parts by weight of lactose monohydrate. The blend was micronised using a high pressure air jet mill and then conditioned using the process of EP-A-717 616. 200 Parts by weight of micronised budesonide was added to the conditioned product by mixing and homogenising with a low pressure jet mill. The mixture was then spheronised using the process of EP-A-721 331 and filled into the storage compartment of a Turbuhaler.

Example 2

4.5 Parts by weight of formoterol fumarate dihydrate was mixed with 835 parts by weight of lactose monohydrate. The blend was micronised using a high pressure air jet mill and then conditioned using the process of EP-A-717 616. 160 Parts by weight of micronised budesonide was added to the conditioned product by mixing and homogenising with a low pressure jet mill. The mixture was then spheronised using the process of EP-A-721 331 and filled into the storage compartment of a Turbuhaler.

Example 3

12 Parts by weight of formoterol fumarate dihydrate was mixed with 588 parts by weight of lactose monohydrate. The blend was micronised using a high pressure air jet mill and then conditioned using the process of EP-A-717 616. 400 Parts by weight of micronised budesonide was added to the conditioned product by mixing and homogenising with a low pressure jet mill. The mixture was then spheronised using the process of EP-A-721 331 and filled into the storage compartment of a Turbuhaler.

Example 4

6 Parts by weight of formoterol fumarate dihydrate was mixed with 894 parts by weight of lactose monohydrate. The blend was micronised using a high pressure air jet mill and then conditioned using the process of EP-A-717 616. 100 Parts by weight of micronised budesonide was added to the conditioned product by mixing and homogenising with a low

pressure jet mill. The mixture was then spheronised using the process of EP-A-721 331 and filled into the storage compartment of a Turbuhaler.

Example 5

4.5 Parts by weight of formoterol fumarate dihydrate was mixed with 915 parts by weight of lactose monohydrate. The blend was micronised using a high pressure air jet mill and then conditioned using the process of EP-A-717 616. 80 Parts by weight of micronised budesonide was added to the conditioned product by mixing and homogenising with a low pressure jet mill. The mixture was then spheronised using the process of EP-A-721 331 and filled into the storage compartment of a Turbuhaler.

Example 6

12 Parts by weight of formoterol fumarate dihydrate was mixed with 788 parts by weight of lactose monohydrate. The blend was micronised using a high pressure air jet mill and then conditioned using the process of EP-A-717 616. 200 Parts by weight of micronised budesonide was added to the conditioned product by mixing and homogenising with a low pressure jet mill. The mixture was then spheronised using the process of EP-A-721 331 and filled into the storage compartment of a Turbuhaler.

Example 7

6 Parts by weight of formoterol fumarate dihydrate was mixed with 994 parts by weight of lactose monohydrate. The blend was micronised using a high pressure air jet mill and then conditioned using the process of EP-A-717 616. The mixture was then spheronised using the process of EP-A-721 331 and filled into the storage compartment of a Turbuhaler.

200 Parts by weight of micronised budesonide was mixed with 800 parts by weight of lactose monohydrate. The blend was micronised using a high pressure air jet mill and then conditioned using the process of EP-A-717 616. The mixture was then spheronised using the process of EP-A-721 331 and filled into the storage compartment of a Turbuhaler.

Example 8

4.5 Parts by weight of formoterol fumarate dihydrate was mixed with 995 parts by weight of lactose monohydrate. The blend was micronised using a high pressure air jet mill and then conditioned using the process of EP-A-717 616. The mixture was then spheronised using the process of EP-A-721 331 and filled into the storage compartment of a Turbuhaler.

160 Parts by weight of micronised budesonide was mixed with 840 parts by weight of lactose monohydrate. The blend was micronised using a high pressure air jet mill and then conditioned using the process of EP-A-717 616. The mixture was then spheronised using the process of EP-A-721 331 and filled into the storage compartment of a Turbuhaler.

Example 9

12 Parts by weight of formoterol fumarate dihydrate was mixed with 988 parts by weight of lactose monohydrate. The blend was micronised using a high pressure air jet mill and then conditioned using the process of EP-A-717 616. The mixture was then spheronised using the process of EP-A-721 331 and filled into the storage compartment of a Turbuhaler.

400 Parts by weight of micronised budesonide was mixed with 600 parts by weight of lactose monohydrate. The blend was micronised using a high pressure air jet mill and then conditioned using the process of EP-A-717 616. The mixture was then spheronised using the process of EP-A-721 331 and filled into the storage compartment of a Turbuhaler.

Example 10

6 Parts by weight of formoterol fumarate dihydrate was mixed with 994 parts by weight of lactose monohydrate. The blend was micronised using a high pressure air jet mill and then conditioned using the process of EP-A-717 616. The mixture was then spheronised using the process of EP-A-721 331 and filled into the storage compartment of a Turbuhaler.

100 Parts by weight of micronised budesonide was mixed with 900 parts by weight of lactose monohydrate. The blend was micronised using a high pressure air jet mill and then conditioned using the process of EP-A-717 616. The mixture was then spheronised using the process of EP-A-721 331 and filled into the storage compartment of a Turbuhaler.

Example 11

4.5 Parts by weight of formoterol fumarate dihydrate was mixed with 995 parts by weight of lactose monohydrate. The blend was micronised using a high pressure air jet mill and then conditioned using the process of EP-A-717 616. The mixture was then spheronised using the process of EP-A-721 331 and filled into the storage compartment of a Turbuhaler.

80 Parts by weight of micronised budesonide was mixed with 920 parts by weight of lactose monohydrate. The blend was micronised using a high pressure air jet mill and then conditioned using the process of EP-A-717 616. The mixture was then spheronised using the process of EP-A-721 331 and filled into the storage compartment of a Turbuhaler.

Example 12

12 Parts by weight of formoterol fumarate dihydrate was mixed with 988 parts by weight of lactose monohydrate. The blend was micronised using a high pressure air jet mill and then conditioned using the process of EP-A-717 616. The mixture was then spheronised using the process of EP-A-721 331 and filled into the storage compartment of a Turbuhaler.

200 Parts by weight of micronised budesonide was mixed with 800 parts by weight of lactose monohydrate. The blend was micronised using a high pressure air jet mill and then conditioned using the process of EP-A-717 616. The mixture was then spheronised using the process of EP-A-721 331 and filled into the storage compartment of a Turbuhaler.

Example A

Patients suffering from COPD are first put through a run-in period of 2 weeks and are then split into 4 groups of approximately equal numbers. Each group is then given either budesonide/formoterol, budesonide alone, formoterol alone or placebo for a period of 12 months.

The following parameters for each patient are monitored throughout: mild and severe exacerbations, FEV_1 (forced expiratory volume in one second), vital capacity (VC), peak expiratory flow (PEF), symptom scores and Quality of Life. Of these, mild and severe exacerbations are considered to be primary efficacy variables, whereas the remaining parameters are considered to be secondary efficacy variables.